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(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

Surf + paracetamol

(54) Medicinal Aerosol Formulation

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Description

A medicinal aerosol formulation

Modern aerosol technology, which is predominantly based
5 on the use of liquefiable safety propellants under moderate pressure, has a number of significant advantages and, furthermore, has opened up numerous novel possibilities of use. The following advantages should be specifically emphasized:

10 Each compressed gas pack is an automatic device which allows, by finger pressure on an applicator, the product to be removed or applied in a form suitable for optimal effect. Using this control it is possible easily, and thus also economically, to divide up the quantity of
15 product to be used. Where it is appropriate for a small dose which is always the same to be removed, a metering valve undertakes this quantity limitation automatically.

The convenience of handling of compressed gas packs of this type is a crucial advantage of this medicinal form.
20 The one-hand devices are practical to use and simple to handle. The automatically closing valve means that the contents cannot run out or be spilt. Volatile substances cannot evaporate, and the contents cannot dry out. The gas-tight closure of the pack prevents entry of air and
25 hence the possible contamination by dust, moisture or germs.

Oxidation-sensitive products can be packaged with exclusion of atmospheric oxygen. A compressed gas pack also provides excellent protection from light for sensi-
30 tive active substances.

Th product packed in the compressed gas packs is frequently composed of a powdered substance (for example a

m dicinal substance) which is suspended in the liquefied propellant, and of a surface-active substance which is used to stabilize the suspension, for example sorbitan trioleate, oleic acid or lecithin. The propellants used to date for medicinal aerosols have been almost exclusively chlorofluorocarbons, eg. trichlorofluoromethane (®Frigen 11), dichlorodifluoromethane (Frigen 12), 1,2-dichlorotetrafluoroethane (Frigen 114), and mixtures thereof. The powder, which must have the smallest possible particle size in order to prevent sedimentation, is dispersed in a considerably larger quantity of propellant. The proportionate quantity of propellant must also be, to reduce the risk of impairments of the valve, at least 85 % by weight and will, in many cases, be considerably above this value. Aerosols of this type are frequently encountered as inhaler aerosols.

Inhaler aerosols are suitable for administering medicinal substances for the therapy of disorders of the airways, for example the administration of beta-sympathomimetics, steroids, anticholinergics, antihistamines, mast-cell stabilizers such as cromoglicic acid or nedocromil, PAF antagonists, leukotriene antagonists, bradykinin antagonists or potassium channel activators for the local therapy of asthma. Inhaler aerosols are also suitable for the systemic therapy of diseases because the pulmonary epithelium has sufficient permeability for low molecular weight medicinal substances. Pulmonary administration by means of inhaler aerosol is particularly suitable for highly active medicinal substances, for example peptides and proteins such as insulin, LHRH analogs, oxytocin, vasopressin analogs, calcitonin analogs or interferon (compare, for example, Banga and Chien, Int. J. Pharm. 48, 15-50 (1988)). Suspension aerosol formulations of LHRH analogs with chlorofluorocarbon as propellant are described, for example, in EP-A 0 510 731.

Discussions about the cause of the damage to the ozone layer by chlorofluorocarbons (CFCs) have led to the use

of these substances being restricted or, in some cases, even prohibited in many countries. It is known from investigations that one of the causes leading to damage to the ozone layer is the reaction of ozone with free radicals produced from chlorine atoms in the CFCs. This is why non-ozone-damaging propellants, for example carbon dioxide, dinitrogen oxide, dimethyl ether, short-chain hydrocarbons (propane or butane) or hydrogenated fluorocarbons (HFCs) have been used recently for aerosols.

Particularly suitable propellants for pharmaceutical aerosols are those propellant gases which can be liquefied under pressure at room temperature and, on inhalation or topical use, are safe, toxicologically innocuous and free of side effects. These properties relate in particular to hydrogenated fluorocarbons (HFCs) such as, for example, tetrafluoroethane (R134a) and heptafluoropropane (R227), with heptafluoropropane being more suitable, because of its lower vapor pressure at room temperature, of about 4 bar, because it is possible to dispense with a pressure-reducing additive. Tetrafluoroethane cannot, because of its higher vapor pressure of 6 bar at room temperature, be used as sole propellant because at 50°C it exceeds the maximum permissible pressure of 12 bar specified in the TRG300 (industrial guidelines on gases) for aluminum cans with a pressure of about 13 bar.

The technology hitherto used to produce medicinal suspension aerosols is based on a solubility of the surface-active substances in the liquefied propellant (the medicinal substance is suspended in the propellant). This property no longer exists on use of novel, alternative propellants such as tetrafluoroethane or heptafluoropropane, because of their higher polarity. This means that formulations with chlorofluorocarbons cannot be modified simply by replacing the propellant by hydrogenated fluorocarbons as described in EP-A 0 513 099, EP-A 0 518 600, EP-A 0 518 601 and EP-A 0 550 031. It is

not possible in this way to produce stable suspensions with the surface-active substances used hitherto in inhaler aerosols.

Hence, according to EP-B 0 372 777 and EP-A 0 499 344, cosolvents with a higher polarity, such as, for example, ethanol, are used to achieve a sufficient solubility of the surface-active substance in the liquefied propellant (HFC). The use of other surface-active substances which dissolve in the liquefied propellant (HFC) but have not hitherto been used in medicinal aerosols is described in EP-A 0 504 112 (monoacetylated or diacetylated monoglycerides), EP-A 0 536 204, EP-A 0 513 127 and EP-A 0 526 481 (fluorinated surfactants), EP-A 0 536 235 (block copolymers of ethylene oxide and propylene oxide as well as polysorbates) and EP-A 0 534 731 (polyvinylpyrrolidone and polyvinyl alcohol). However, the said substances have the crucial disadvantage that they have not undergone toxicological testing for inhalation use or in fact have proved unsuitable because tissue-damaging.

Furthermore, the Patent Applications WO 92/08446 and WO 92/08447 describe a process in which active substances are coated with the surface-active substance. This process starts from an active substance which is already micronized, and is suspended in a solution of the surface-active substance in an organic solvent, such as, for example, isopentane, in which the active substance is virtually insoluble. After a certain time, the solvent is removed. The active substances modified in this way can be suspended in hydrogenated fluorocarbons (HFCs), where appropriate with the addition of a cosolvent. One disadvantage of this process is that the previously micronized active substance must be suspended and redried. Agglomeration of the particles may occur during this. The process does not ensure uniform dispersion of the surface-active substance. The use of an additional organic solvent such as isopentane must also be judged negatively.

The invention was thus based on the object of formulating a stable suspension metered aerosol for medicinal use containing a pharmaceutical active substance, a physiologically tolerated surface-active substance which is insoluble in the liquefied propellant, for example sorbitan trioleate, oleic acid and lecithin, where appropriate a masking flavor, for example a sweetener such as saccharin, acesulfame K or aspartame, or an essential oil, where appropriate a generally customary ancillary substance from the group of sugars or sugar alcohols, such as lactose, glucose or mannitol, and as propellant a hydrogenated fluorocarbon, preferably heptafluoropropane (R227).

The object is achieved according to the invention by converting the active substance and surface-active substance, where appropriate with the said additional ancillary substances, by spray drying into a form in which they are present finely dispersed together in a matrix. It has been found, surprisingly, that this spray-dried product subsequently forms, without further additives, a fine, stable, homogeneous suspension in the liquefied propellant.

The invention therefore relates to a medicinal substance preparation in the form of a suspension aerosol, which comprises

- a) a spray-dried product composed of a medicinal substance and of a physiologically tolerated surface-active substance which is insoluble in the liquefied propellant, and, where appropriate, a masking flavor and, where appropriate, a generally customary physiologically tolerated auxiliary substance and
- b) a liquefiable, hydrogenated or partially hydrogenated fluorocarbon as propellant.

The active substances and ancillary substances (including surface-active substances) are present finely dispersed in a matrix in the spray-dried product. Addition of the

propellant results in a fine, stable, homogeneous suspension. The product particles have a particle size customary for aerosols.

5 The invention furthermore relates to a process for the production of a medicinal substance preparation in the form of a suspension aerosol, which comprises dissolving the medicinal substance, the physiologically tolerated surface-active substance and, where appropriate, a masking flavor and, where appropriate, other generally
10 customary physiologically tolerated auxiliary substances in a suitable solvent, subjecting the resulting solution to a spray drying, metering the spray-dried product into a compressed gas pack, closing the latter with a metering valve, and metering in the quantity of the liquefiable,
15 hydrogenated or partially hydrogenated fluorocarbon required to form the suspension aerosol.

Suitable medicinal substances are those which act locally on the lung and are suitable for inhalation, that is to say, for example, medicinal substances for the treatment
20 of airway disorders or asthma, such as beta-sympathomimetics, steroids, anticholinergics, antihistamines, antiallergics, mast-cell stabilizers such as cromoglicic acid or nedocromil, PAF antagonists, leukotriene antagonists, bradykinin antagonists or potassium channel
25 activators.

The spray drying is also suitable for pharmaceutical active substances which cannot be micronized by conventional methods such as milling and thus converted into a particle size necessary for inhalation. This particularly
30 applies to peptides and proteins obtained by freeze drying and in amorphous form.

Suitable active substances are therefore also peptides and proteins of natural or synthetic origin and their physiologically tolerated salts. Examples which may be
35 mentioned are: insulins, LHRH analogs, oxytocin,

vasopressin analogs, calcitonin analogs and interferon and their physiologically tolerated salts.

5 The suspension aerosols according to the invention preferably contain as medicinal substance an insulin, a bradykinin antagonist, an LHRH analog such as buserelin or their physiologically tolerated salts.

10 The suspension aerosols according to the invention are particularly suitable for asthma treatment and contain, for example, the bradykinin antagonist icatibant (= H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH (HOE 140)) or an icatibant salt or the potassium channel activator rilimakalim ((+)-(3S,4R)-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-6-phenyl-sulfonylchroman hemihydrate).

15 Particularly preferred surface-active substances are sorbitan trioleate, oleic acid or lecithin. Suitable as lecithin are all natural lecithins such as egg or soybean lecithin, partially hydrogenated and hydrogenated lecithins, and highly purified phosphatidylcholines.

20 Examples of suitable masking flavors are sweeteners such as saccharin, aspartame and acesulfame K, or essential oils.

25 The generally customary physiologically tolerated ancillary substances must, just like the active substances, surface-active substances and masking flavors, be soluble in the common solvent. The nature of these ancillary substances therefore depends on the solvent used. Particularly suitable ancillary substances are from the group of sugars and sugar alcohols, such as lactose, glucose or mannitol.

30 The spray-dried product contains one or more active substances, one or more surface-active substances and, where appropriate, one or more other ancillary substances and masking flavors.

Examples of suitable propellants are heptafluoropropane (R227) and t trafluoro thane (R134a), preferably mixed with R227.

5 Examples of suitable common solvents for the ingredients in the spray-dried product are mixtures of lower alcohols (with up to 6 carbon atoms) or ketones with water.

The content of active substance in the spray-dried product depends in particular on the level of dosage required.

10 The content of surface-active substance dispersed in the active substance matrix is relatively small and is, for example, from 0.01 to 1.0 % by weight, preferably from 0.05 to 0.5 % by weight, based on the content of active substance.

15 The spray-drying is carried out by conventional methods as described in the literature (compare, for example, J. Broadhead et al., Drug Development and Industrial Pharmacy, 18, 1169-1206 (1992)). It is preferably carried out at elevated temperature, the level depending, inter
20 alia, on the active substance and solvent used.

The spray-drying process confers on the active substance particles a spherical aerodynamic shape which favors movement in the airstream during inhalation and thus increases the proportion of particles entering the lungs.
25 In addition, adhesion and agglomeration forces both in the suspension and during the spraying-out process are reduced. The spray-drying process to produce powders to be used for inhalation has already been disclosed in the Patents GB 1 520 248 and GB 1 569 612. However, in these
30 cases only the pure active substances were spray dried without addition of surface-active substances, masking flavors or other ancillary substances, and subsequently formulated in the form of a powder inhalant and not as suspension aerosol.

The invention is illustrated by means of the following examples:

Example 1

1968 mg of icatibant acetate, 2.0 mg of soybean lecithin
5 S100 (Lipoid K.G.) and 30 mg of saccharin are converted
into a clear solution in an ethanol/water mixture (25 %
w/w) and spray dried in a spray-drying apparatus at 110°C
under inert conditions (N₂). The product results from
this as a fine white powder. The powder is metered in
10 10 mg portions into an aluminum monobloc can prescribed
for metered aerosols, the can is closed with a metering
valve, and subsequently 10 g of R227 are introduced
through the metering valve. Immediately after the intro-
duction a fine homogeneous suspension of primary medici-
15 nal substance particles in R227 is formed. One actuation
of the inhaler aerosol (suspension aerosol) produced by
the process contains 100 µl of suspension, containing
100 µg of medicinal substance, per administration.

Example 2

20 430 mg of icatibant acetate, 3566 mg of lactose and 4 mg
of hydrogenated egg lecithin (EPC-3, Lipoid K.G.) are
converted into a clear solution in an ethanol/water
mixture (25 % w/w) and spray dried in a spray-drying
apparatus at 90°C under inert conditions (N₂). The
25 product results from this as a fine white powder. The
powder is metered in 10 mg portions into an aluminum
monobloc can prescribed for metered aerosols, the can is
closed with a metering valve, and subsequently 10 g of
R227 are introduced through the metering valve. Immedi-
30 ately after the introduction a fine homogeneous suspen-
sion of primary medicinal substance particles in R227 is
formed. One actuation of the inhaler aerosol (suspension
aerosol) produced by the process contains 100 µl of
suspension, containing 10 µg of medicinal substance, per
35 administration.

Example 3

1968 mg of icatibant acetate, 2 mg of sorbitan trioleate and 30 mg of aspartame are converted into a clear solution in an ethanol/water mixture (25 % w/w) and spray
5 dried in a spray-drying apparatus at 110°C under inert conditions (N₂). The product results from this as a fine white powder. The powder is metered in 10 mg portions into an aluminum monobloc can prescribed for metered aerosols, the can is closed with a metering valve, and
10 subsequently 10 g of R227 are introduced through the metering valve. Immediately after the introduction a fine homogeneous suspension of primary medicinal substance particles in R227 is formed. One actuation of the inhaler aerosol (suspension aerosol) produced by the process
15 contains 100 µl of suspension, containing 100 µg of medicinal substance, per administration.

Example 4

1000 mg of human insulin, 2 mg of soybean lecithin S100 and 1000 mg of lactose are converted into a clear solution in an ethanol/water mixture (25 % w/w) and spray
20 dried in a spray-drying apparatus at 90°C under inert conditions (N₂). The product results from this as a fine white powder. The powder is metered in 50 mg portions into an aluminum monobloc can prescribed for metered aerosols, the can is closed with a metering valve, and
25 subsequently 10 g of R227 are introduced through the metering valve. Immediately after the introduction a fine homogeneous suspension of primary medicinal substance particles in R227 is formed. One actuation of the inhaler aerosol (suspension aerosol) produced by the process
30 contains 100 µl of suspension, corresponding to 3 I.U. of insulin, per administration.

Example 5

1998 mg of buserelin acetate and 2 mg of soybean lecithin

S100 are converted into a clear solution in an ethanol/water mixture (25 % w/w) and spray dried in a spray-drying apparatus at 90°C under inert conditions (N₂). The product results from this as a fine white powder. The powder is metered in 10 mg portions into an aluminum monobloc can prescribed for metered aerosols, the can is closed with a metering valve, and subsequently 10 g of R227 are introduced through the metering valve. Immediately after the introduction a fine homogeneous suspension of primary medicinal substance particles in R227 is formed. One actuation of the inhaler aerosol (suspension aerosol) produced by this process contains 100 µl of suspension, containing 100 µg of medicinal substance, per administration.

Example 6

1998 mg of rilimakalim hemihydrate and 2.0 mg of soybean lecithin S100 are converted into a clear solution in an ethanol/water mixture (50 % w/w) and spray dried in a spray-drying apparatus at 100°C under inert conditions (N₂). The product results from this as a fine white powder. The powder is metered in 100 mg portions into an aluminum monobloc can prescribed for metered aerosols, the can is closed with a metering valve, and subsequently 10 g of R227 are introduced through the metering valve. Immediately after the introduction a fine homogeneous suspension of primary medicinal substance particles in R227 is formed. One actuation of the inhaler aerosol (suspension aerosol) produced by this process contains 100 µl of suspension, containing 1000 µg of medicinal substance, per administration.

Example 7

1998 mg of icatibant acetate and 2.0 mg of sorbitan trioleat (Span®85) are converted into a clear solution in an ethanol/water mixture (25 % w/w) and spray dried in a spray-drying apparatus at 100°C under inert conditions

(N₂). The product results from this as a fine white powder. The powder is metered in 10 mg portions into an aluminum monobloc can prescribed for metered aerosols, the can is closed with a metering valve, and subsequently 10 g of R227 are introduced through the metering valve. Immediately after the introduction a fine homogeneous suspension of primary medicinal substance particles in R227 is formed. One actuation of the inhaler aerosol (suspension aerosol) produced by this process contains 100 µl of suspension, containing 100 µg of medicinal substance, per administration.

Example 8

1998 mg of icatibant acetate and 2.0 mg of oleic acid are converted into a clear solution in an acetone/water mixture (25 % w/w) and spray dried in a spray-drying apparatus at 80°C under inert conditions (N₂). The product results from this as a fine white powder. The powder is metered in 10 mg portions into an aluminum monobloc can prescribed for metered aerosols, the can is closed with a metering valve, and subsequently 10 g of R227 are introduced through the metering valve. Immediately after the introduction a fine homogeneous suspension of primary medicinal substance particles in R227 is formed. One actuation of the inhaler aerosol (suspension aerosol) produced by this process contains 100 µl of suspension, containing 100 µg of medicinal substance, per administration.

Example 9

200 mg of salbutamol, 2.0 mg of soybean lecithin S100 and 1798 mg of lactose are converted into a clear solution in an ethanol/water mixture (25 % w/w) and spray dried in a spray-drying apparatus at 80°C under inert conditions (N₂). The product results from this as a fine white powder. The powder is metered in 50 mg portions into an aluminum monobloc can prescribed for metered aerosols,

th can is closed with a metering valve, and subsequently 10 g of R227 are introduced through the metering valve. Immediately after the introduction a fine homogeneous suspension of primary medicinal substance particles in R227 is formed. One actuation of the inhaler aerosol (suspension aerosol) produced by this process contains 100 μ l of suspension, containing 50 μ g of medicinal substance, per administration.

Example 10

10 1998 mg of prednisolone and 2.0 mg of soybean lecithin S100 are converted into a clear solution in an ethanol-water mixture (50 % w/w) and spray dried in a spray-drying apparatus at 80°C under inert conditions (N_2). The product results from this as a fine white powder. The powder is metered in 10 mg portions into an aluminum monobloc can prescribed for metered aerosols, the can is closed with a metering valve, and subsequently 10 g of R227 are introduced through the metering valve. Immediately after the introduction a fine homogeneous suspension of primary medicinal substance particles in R227 is formed. One actuation of the inhaler aerosol (suspension aerosol) produced by this process contains 100 μ l of suspension, containing 100 μ g of medicinal substance, per administration.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A medicinal substance preparation in the form of a suspension aerosol, which comprises

- 5 a) a spray-dried product composed of a medicinal substance and of a physiologically tolerated surface-active substance which is insoluble in the liquefied propellant, and, where appropriate, a masking flavor and, where appropriate, a generally customary physiologically tolerated auxiliary substance and
- 10 b) a liquefiable, hydrogenated or partially hydrogenated fluorocarbon as propellant.

2. A process for the production of a medicinal substance preparation in the form of a suspension aerosol as claimed in claim 1, which comprises dissolving the medicinal substance, the physiologically tolerated surface-active substance and, where appropriate, a masking flavor and, where appropriate, other generally customary physiologically tolerated auxiliary substances in a suitable solvent, subjecting the resulting solution to a spray drying, metering the spray-dried product into a compressed gas pack, closing the latter with a metering valve, and metering in the quantity of the liquefiable, hydrogenated or partially hydrogenated fluorocarbon required to form the suspension aerosol.
- 15
- 20

3. A medicinal substance preparation as claimed in claim 1, which comprises medicinal substances suitable for inhalation and acting locally on the lung for the treatment of airway disorders or asthma.
- 25

4. A medicinal substance preparation as claimed in claim 1, which comprises as medicinal substance a peptide or protein or physiologically tolerated salts thereof.

5. A medicinal substance preparation as claimed in claim 1, which comprises icatibant or its physiologically tolerated salt.
- 5 6. A medicinal substance preparation as claimed in claim 1, wherein the surface-active substance is sorbitan trioleate, oleic acid or lecithin.
7. A medicinal substance preparation as claimed in claim 1, wherein the propellant is heptafluoropropane.
- 10 8. A medicinal substance preparation as claimed in claim 1, wherein the masking flavor is a sweetener and/or an essential oil, and the other ancillary substances are selected from the group of sugars and sugar alcohols.

Abstract of the disclosure

A medicinal aerosol formulation

- 5 The invention related to a medicinal substance preparation in the form of a suspension aerosol which comprises a spray-dried product which is composed of a medicinal substance, of a surface-active, physiologically tolerated substance which is insoluble in the liquefied propellant, where appropriate a masking flavor and/or a customary auxiliary substance, in a liquefiable, hydrogenated or partially hydrogenated
- 10 fluorocarbon as propellant. The invention furthermore relates to a process for the production of the medicinal substance preparation which comprises medicinal substances suitable for inhalation and acting locally on the lung for the treatment of airway disorders or asthma.